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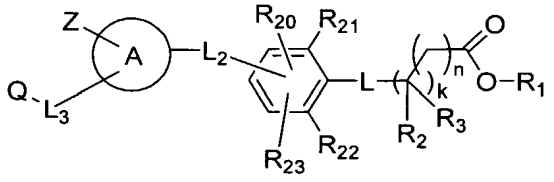

(I)

(57) Abstract: The present invention relates to compounds and pharmaceutically acceptable salts of formula: (I) which are useful in the treatment of metabolic disorders related to insulin resistance or hyperglycemia. These compounds include inhibitors of protein tyrosine phosphatase (PTP-1B) that are useful in the treatment of diabetes and other PTP-1B mediated diseases, such as cancer, neurodegenerative diseases and the like. The compounds of the invention are also useful in pharmaceutical compositions and methods of treating the aforementioned conditions.

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Substituted Phenylalkanoic acids

BACKGROUND OF THE INVENTION

This application claims priority from U.S. Provisional Application Serial Nos. 60/624318 and 60/623659, both of which were filed October 28, 2004, and both of which are incorporated herein by reference in their entirety.

Field of the Invention

The invention relates to substituted phenylalkanoic acids that are useful in the treatment of diabetes. More specifically, it relates to such compounds that are capable of inhibiting Protein tyrosine phosphatase-1B (PTP-1B), which is a negative regulator of the insulin signaling pathway, and improves insulin-sensitivity.

Description of the Related Art

Protein tyrosine phosphatases are a large family of transmembrane or intracellular enzymes that dephosphorylate substrates involved in a variety of regulatory processes (Fischer et al., 1991, Science 253:401-406). Protein tyrosine phosphatase-1B (PTP-1B) is an approximately 50 kd intracellular protein, which is present in abundant amounts in various human tissues (Charbonneau et al., 1989, Proc. Natl. Acad. Sci. USA 86:5252-5256; Goldstein, 1993, Receptor 3:1-15).

Determining which proteins are substrates of PTP-1B has been of considerable interest. One substrate which has aroused especial interest is the insulin receptor. The binding of insulin to its receptor results in autophosphorylation of the domain. This causes activation of the insulin receptor tyrosine kinase, which phosphorylates the various insulin receptor substrate (IRS) proteins that propagate the insulin signaling event further downstream to mediate insulin's various biological effects.

Seely et al., 1996, Diabetes 45:1379-1385 ("Seely") studied the relationship of PTP-1B and the insulin receptor in

vitro. Seely constructed a glutathione S-transferase (GST) fusion protein of PTP-1B that had a point mutation in the PTP-1B catalytic domain. Although catalytically inactive, this fusion protein was able to bind to the insulin receptor, as demonstrated by its ability to precipitate the insulin receptor from purified receptor preparations and from whole cell lysates derived from cells expressing the insulin receptor.

Ahmad et al., 1995, J. Biol. Chem. 270:20503-20508 used osmotic loading to introduce PTP-1B neutralizing antibodies into rat KRC-7 hepatoma cells. The presence of the antibody in the cells resulted in an increase of 42% and 38%, respectively, in insulin stimulated DNA synthesis and phosphatidyinositol 3' kinase activity. Insulin receptor autophosphorylation and insulin receptor substrate-1 tyrosine phosphorylation were increased 2.2 and 2.0-fold, respectively, in the antibody-loaded cells. The antibody-loaded cells also showed a 57% increase in insulin stimulated insulin receptor kinase activity toward exogenous peptide substrates.

Kennedy et al., 1999, Science 283: 1544-1548 showed that protein tyrosine phosphatase PTP-1B is a negative regulator of the insulin signaling pathway, indicating that inhibitors of this enzyme are beneficial in the treatment of Type 2 diabetes, which appears to involve a defect in an early process in insulin signal transduction rather than a structural defect in the insulin receptor itself. (J. M. Olefsky, W. T. Garvey, R. R. Henry, D. Brillon, S. Matthai and G. R. Freidenberg, G. R. (1988).) Cellular mechanisms of insulin resistance in non-insulin-dependent (Type II) diabetes. (Am. J. Med. 85: Suppl. 5A, 86-105.) A drug that improved insulin sensitivity would have several advantages over traditional therapy of NIDDM using sulfonylureas, which do not alleviate insulin resistance but instead compensate by increasing insulin secretion.

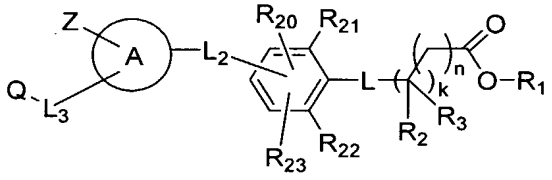
Therefore, inhibitors of PTP-1B are useful in controlling or treating Type 2 diabetes, in improving glucose tolerance,

and in improving insulin sensitivity in patients in need thereof. The compounds are also useful in treating or controlling other PTP-1B mediated diseases, such as the treatment of cancer, neurodegenerative diseases and the like.

SUMMARY OF THE INVENTION

In a broad aspect, the invention encompasses the compounds of formula (I) shown below, pharmaceutical compositions containing the compounds and methods employing such compounds or compositions in the treatment of diabetes.

In one aspect, the invention encompasses compounds formula I:



I

and pharmaceutically acceptable salts thereof, wherein,

k is 0 or 1;

n is 0, 1, 2, or 3;

each R_1 is independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, or C_3-C_6 alkenyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-heterocycloalkyl, -(C_1-C_4) alkyl-heteroaryl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H or $-CO_2R_1$,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, arylalkoxy, arylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, NH-aryl, $-N(C_1-C_4$ alkyl$)C(O)$aryl, $-NHC(O)$aryl, NHarylalkyl, $NHC(O)-(C_1-C_4)$ alkyl-aryl, $N(C_1-C_4$ alkyl$)C(O)-(C_1-C_4)$ alkyl-aryl, $N(C_1-C_4)$alkyl-aryl, $-NHSO_2$-aryl, $-N(C_1-C_4$alkyl$)SO_2$aryl, or $-N(C_1-C_4$alkyl)arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy;

L is $-C_2-C_6$ alkenyl-, - or C_2-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy;

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl$-C(O)NR_9-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl-, $-N(R_9)C(O)$ $-(C_1-C_4)$alkyl-, $-(C_1-C_4)$alkyl$-C(O)N(R_9)-(C_1-C_4)$alkyl-, $-(C_1-C_4)$alkyl$-N(R_9)C(O)$ $-(C_1-C_4)$alkyl-, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R9)-$, $-N(R_9)-(C_1-C_4)$alkyl-, $-O-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-O-$, or $-(C_1-C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, $-SO_2$aryl, arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, $-(C_1-C_4)$alkyl$-O-$, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$ alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, furanyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, pyridyl, quinolinyl, naphthyl, quinazolinyl,

benzo[b]thiophene, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, CN, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, cycloalkyl, aryl, -aryl-carbonyl-aryl, -aryl-alkyl-aryl, -aryl-heteroaryl, -aryl-heterocycloalkyl, -heteroaryl, -heteroaryl-alkyl-aryl, -heterocycloalkyl, -aryl-O-aryl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, aryl$(C_1$-$C_6)$alkyl, alkanoyl, arylalkanoyl, alkoxycarbonyl, arylalkoxycarbonyl, heteroarylcarbonyl, heteroaryl, heterocycloalkylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, or $-SO_2$-aryl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, haloalkyl or haloalkoxy, and

Z is absent, H, -NHC(O)aryl, $-N(C_1$-C_4 alkyl$)C(O)$aryl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, or NO_2, or

Z is $-NHC(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl, $-N(C_1$-$C_4)$alkyl$C(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl;

provided that when L_2 is a bond, the A ring is not phenyl.

Compounds of formula I bind to PTP-1B. Preferably that interaction results in inhibition of the enzyme.

The invention also includes intermediates that are useful in making the compounds of the invention.

The invention also provides pharmaceutical compositions comprising a compound or salt of formula I and at least one pharmaceutically acceptable carrier, solvent, adjuvant or diluent.

The invention further provides methods of treating disease in a patient in need of such treatment, comprising administering a compound or pharmaceutically acceptable salt of formula I, or a pharmaceutical composition comprising a compound or salt of formula I.

In another aspect, the invention provides a method for inhibiting protein tyrosine phosphatase comprising administering a therapeutically effective amount of a compound of formula I.

In another aspect, the invention provides a method for treating metabolic disorders related to insulin resistance or hyperglycemia, comprising administering a therapeutically effective amount of a compound of formula I.

The invention also provides the use of a compound or salt according to formula I for the manufacture of a medicament.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

The invention also provides methods and compositions for combination therapy of Type I and Type II diabetes. In these embodiments, the invention provides formulations and pharmaceutical compositions, as well as methods for treating Type I and Type II diabetes with the PTPase inhibitors of formula I plus additional compounds and medicaments as disclosed in more detail below. In these embodiments, the methods of the invention can comprise treatment methods for

Type I and Type II diabetes where the PTPase inhibitors of formula I are formulated with a therapeutically-effective amount of said additional compounds and medicaments. In alternative embodiments, treatment methods of the invention for Type I and Type II diabetes comprise administration of the inventive PTPase inhibitors of formula I as disclosed herein concomitantly, simultaneously or together with a therapeutically-effective amount of said additional compounds and medicaments.

DETAILED DESCRIPTION OF THE INVENTION

A preferred class of compounds of formula I are compounds of formula I-1, wherein

R_1 is H, C_1-C_6 alkyl, benzyl, or allyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-pyridinyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, or -(C_1-C_4) alkyl-tetrahydrofuranyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy,

haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, benzofuranyl, benzothienyl, pyrrolyl, imidazolyl, adamantanyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, dibenzofuranyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, dihydroquinolinyl, dihydroisoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1-C_6)$alkyl, $-C(O)N(C_1-C_6)$alkyl(C_1-C_6)alkyl, or $-SO_2$-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is H, absent, -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Particularly preferred compounds of formula I are those where R_1 is H. Compounds of formula I having R_1 groups that are C_1-C_6 alkyl, benzyl and allyl are preferred as intermediates.

A preferred group of compounds are those where k is 0. When k is 0, R_2 group and the methylene carrying it are absent.

Another preferred group of compounds are those where k is 1. When k is 1, R_2 is present.

A particularly preferred Q group is adamantanyl. Another preferred Q group is dibenzofuranyl, more preferably dibenzofuran-3-yl or dibenzofuran-4-yl, most preferably dibenzofuran-4-yl. Each of these preferred Q groups is optionally substituted with from 1-4, more preferably 1-3, and most preferably 1-3 groups selected from C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, and NR_6R_7, where R_6 and R_7 are independently H, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, piperidinyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, -C(O)NH(C_1-C_6)alkyl, or -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl.

Other preferred Q groups include 3,4-dihydroisoquinolin-1-yl and 1,2,3,4-tetrahydroisoquinolin-2-yl. Each of these is optionally substituted with from 1-4, more preferably 1-3, and most preferably 1-3 groups selected from C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, and NR_6R_7, where R_6 and R_7 are independently H, C_1-C_6 alkyl, C_1-

C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, piperidinyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1-C_6)$alkyl, and $-C(O)N(C_1-C_6)$alkyl(C_1-C_6)alkyl.

Also preferred are compounds wherein R_2 is H.

Preferred compounds of formula I also include compounds wherein L_2 is in a meta position on the phenylene ring relative to L.

Preferred compounds of formula I further include compounds wherein L_2 is in the para position on the phenylene ring relative to L.

Preferred compounds of formula I-1 include compounds of formula I-2, wherein

L is $-C_2$-C_6 alkenyl- or $-C_2$-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl$-C(O)NR_9-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl$-$, $-N(R_9)C(O)-(C_1-C_4)$alkyl$-$, $-(C_1-C_4)$alkyl$-C(O)N(R_9)-(C_1-C_4)$alkyl$-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-(C_1-C_4)$alkyl$-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R9)-$, $-N(R_9)-(C_1-C_4)$alkyl$-$, $-O-(C_1-C_4)$alkyl$-$, $-(C_1-C_4)$alkyl$-O-$, or $-(C_1-C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, anthracenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, $-(C_1-C_4)$alkyl$-O-$, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$ alkyl$-$, $-C(O)-$; and

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, -NHC(O)-(C_1-C_4) alkyl-phenyl, -N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-phenyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy.

Preferred compounds of formula I-2 include compounds of formula I-3, wherein

L is -C_2-C_6 alkenyl- or -C_2-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -C(O)N(R_9)-(C_1-C_4)alkyl-, -N(R_9)C(O) -(C_1-C_4)alkyl-,-N(R_9)SO_2-, -SO_2N(R_9)-, -N(R9)-, -N(R_9)-(C_1-C_4)alkyl-, -O-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-O-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -C(O)-;

R_1 is H, C_1-C_6 alkyl, benzyl or allyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4)

alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H;

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, N(C_1-C_4)alkyl-phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, imidazolidinyl, dibenzofuranyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl,

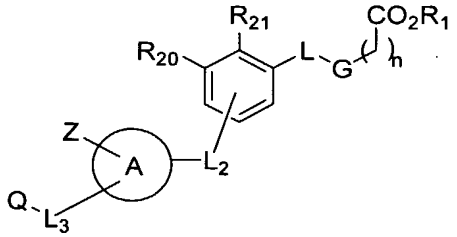
halogen, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is H, absent, -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Preferred compounds or salts of formula I-3 include those compounds of formula II:



II

wherein

G is a bond or C(H)(R_2);

R_1 is H, C_1-C_4 alkyl, or benzyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

R_{10} is H, C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy; and

R_{20}, and R_{21}, are independently selected from H, benzyloxy, benzyl, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, N(C_1-C_4)alkyl-phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy.

Preferred compounds of formula II include compounds wherein L_2 is in a meta position on the phenylene ring relative to L.

Preferred compounds of formula II further include compounds wherein L_2 is in the para position on the phenylene ring relative to L.

Preferred compounds of formula II include compounds of formula II-1, i.e., compounds wherein

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, benzyl, phenethyl, naphthyl-CH_2-, anthracenyl-CH_2-, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -C(O)-;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl-pyridyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, dibenzofuranyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, pyridylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3, and

Z is H, absent, -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Other compounds of formula II-1 include compounds of formula II-2, i.e., compounds wherein

R_1 is H, C_1-C_4 alkyl, or benzyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, wherein the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

R_{10} is H, C_1-C_4 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy; and

R_{20}, and R_{21}, are independently selected from H, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl,

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, benzyl, phenethyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, or -C(O)-;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_2 haloalkoxy, C_1-C_2 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3, and

Z is H, absent, -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Preferred compounds of formula II-2 include compounds of formula II-3, i.e., compounds wherein

R_1 is H, or C_1-C_4 alkyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, wherein the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or -SO_2-(C_1-C_4) alkyl;

R_{10} is H, C_1-C_4 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3; and

at least one of R_{20} and R_{21}, is H, while the other is H, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl,

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, benzyl, phenethyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, or -C(O)-;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, pyrrolidinyl, or piperazinyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, wherein the phenyl groups are optionally substituted

with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3, and

Z is H, absent, -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl (in one aspect, CF_3), C_1-C_2 haloalkoxy (in one aspect, OCF_3), or NO_2, or

Z is $-NHC(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl, or $-N(C_1$-$C_4)$alkyl-$C(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl.

Preferred compounds of formula II-3 include compounds of formula II-4, i.e., compounds wherein

L_2 is a bond or $-NR_9-$; wherein

R_9 is H, C_1-C_6 alkyl, or benzyl;

R_2 is H, phenyl, benzyl, phenethyl, or C_1-C_6 alkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or $-SO_2-(C_1$-$C_4)$ alkyl;

Q is phenyl, or pyridyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_4)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_4)$alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3, and

Z is H, absent, or phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6

alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2.

Preferred compounds of formula II-4 include compounds of formula II-5, i.e., compounds wherein the A ring is pyrazolyl, dihydropyrazolyl, thiazolyl, or pyrimidyl each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In a preferred embodiment, the A ring is unsubstituted or substituted with at least one halogen.

Preferred compounds of formula II-5 include compounds of formula II-6, i.e., compounds wherein R_{10} is H or C_1-C_4 alkyl; and L_3 is a bond or -$(C_1$-$C_4)$ alkyl-. More preferably, R_{10} is H or methyl.

In another aspect, the invention provides compounds of formula II-6-a, i.e., compounds of formula II-5 or II-6 wherein the A ring is pyrazolyl, dihydropyrazolyl, thiazolyl, or pyrimidyl each of which is unsubstituted.

In yet another aspect, the invention provides compounds of formula II-6-b, i.e., compounds of formula II-5, II-6, or II-6-a wherein R_1 is H.

In still another aspect, the invention provides compounds of formula II-6-c, i.e., compounds of formula II-5, II-6, II-6-a, or II-6-b wherein L_3 is a bond, and L_2 is a bond.

In yet another aspect, the invention provides compounds of formula II-6-d, i.e., compounds of formula II-6-c or II-6-b wherein the A ring is pyrazolyl or thiazolyl.

In still yet another aspect, the invention provides compounds of formula II-6-e, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, wherein Z is absent.

In another aspect, the invention provides compounds of formula II-6-f, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, wherein Z is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, C_1-C_2 haloalkyl (in one aspect, CF_3), C_1-C_2 haloalkoxy (in one aspect, OCF_3), or NO_2. In another aspect, the phenyl is optionally substituted with no more than three substituents. In yet another aspect, the phenyl is monosubstituted. In still another aspect, the phenyl ring is unsubstituted.

In yet another aspect, the invention provides compounds of formula II-6-g, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, or II-6-f, wherein Q is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_4)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-h i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-g, wherein Q is phenyl, which is optionally substituted with 1, 2,

or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-i, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-g wherein Q is phenyl, which is optionally substituted with 1, 2, or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, OCF_3 or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), phenyl(C_1-C_2)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_2)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In yet another aspect, the invention provides compounds of formula II-6-j, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, or II-6-f, wherein Q is pyridyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_4)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-k, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-j, wherein Q is pyridyl, which is optionally substituted with 1, 2, or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-l, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-j wherein Q is pyridyl, which is optionally substituted with 1, 2, or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, OCF_3 or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), phenyl(C_1-C_2)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_2)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

Other preferred compounds of formula II-4 include compounds of formula II-7, i.e., compounds wherein

n is 0, 1, 2, or 3;

R_1 is H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, or C_3-C_6 alkenyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-pyridinyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, or -(C_1-C_4) alkyl-tetrahydrofuranyl, wherein

the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H or $-CO_2R_1$,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, phenylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, NH-phenyl, $-N(C_1-C_4$ alkyl$)C(O)$phenyl, $-NHC(O)$phenyl, NHphenylalkyl, $NHC(O)-(C_1-C_4)$ alkyl-phenyl, $N(C_1-C_4$ alkyl$)C(O)-(C_1-C_4)$ alkyl-phenyl, $N(C_1-C_4)$alkyl-phenyl, $-NHSO_2$-phenyl, $-N(C_1-C_4$alkyl$)SO_2$phenyl, or $-N(C_1-C_4$alkyl)phenylalkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy; and

L is $-C_1-C_6$ alkenyl- or $-C_1-C_6$ alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy.

Other preferred compounds of formula II-7 include compounds of formula II-8, i.e., compounds wherein

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl$-C(O)NR_9-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl-, $-N(R_9)C(O)-(C_1-C_4)$alkyl-, $-(C_1-C_4)$alkyl$-C(O)N(R_9)-(C_1-C_4)$alkyl-, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-(C_1-C_4)$alkyl-, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)$alkyl-, $-O-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-O-$, or $-(C_1-C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, -SO_2phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, -$(C_1$-$C_4)$alkyl-O-, -O-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, quinolinyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, furanyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -$(C_1$-$C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-$(C_1$-$C_4)$alkyl-phenyl, -pyrimidyl-$(C_1$-$C_4)$alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy,

halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

Other preferred compounds of formula II-8 include compounds of formula II-9, i.e., compounds wherein

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, benzyl, phenethyl, halogen, C_1-C_6 alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -NHSO_2-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein each of the preceding phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3;

L is -C_1-C_6 alkenyl-, -C_1-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are

independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy; or

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl$-C(O)NR_9-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl$-$, $-N(R_9)C(O)-(C_1-C_4)$alkyl$-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)$alkyl$-$, $-O-(C_1-C_6)$alkyl$-$, $-(C_1-C_6)$alkyl$-O-$, or $-(C_1-C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, $-(C_1-C_4)$alkyl$-O-$, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkyl$-$, -alkenyl-, C(O);

R_1 is H, C_1-C_6 alkyl;

R_2 is H, phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, $-(C_1-C_4)$ alkyl-pyridinyl, (C_1-C_4) hydroxyalkyl, wherein the phenyl ring is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, or pyrrolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, or $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl $-(C_1-C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide,

-phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

In another aspect, the invention provides compounds of formula II-10, i.e., compounds of formula II-9 wherein

R_{22} and R_{23} are both H; and

R_{20}, and R_{21}, are independently H, phenyl(C_1-C_4)alkoxy, benzyl, phenethyl, halogen, C_1-C_6 alkyl, OH, alkoxy, and NO_2, wherein each of the preceding phenyl groups is optionally

substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3;

In another aspect, the invention provides compounds of formula II-11, i.e., compounds of formula II-9 wherein
R_{22} and R_{23} are both H; and
R_{20}, and R_{21}, are independently H, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, NH-phenyl, NHphenylalkyl, $N(C_1$-$C_4)$alkyl-phenyl, $-NHSO_2$-phenyl, $-N(C_1$-C_4alkyl$)SO_2$phenyl, or $-N(C_1$-C_4alkyl$)$phenyl$(C_1$-$C_6)$alkyl, wherein each of the preceding phenyl groups is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3.

In another aspect, the invention provides compounds of formula II-12, i.e., compounds of formula II-10 or II-11 wherein
R_1 is H or methyl (preferably H.)

In another aspect, the invention provides compounds of formula II-13, i.e., compounds of formula II-10, II-11, or 11-12 wherein L is $-C_1$-C_6 alkenyl-, $-C_1$-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, OH, NO_2, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-14, i.e., compounds of formula II-10, II-11, or 11-12 wherein L is $-SO_2NH$-, $-SO_2N(C_1$-$C_4)$ alkyl-, $-NHSO_2$-, -O-, $-C(O)NH$-, $-C(O)N(C_1$-$C_4)$alkyl-, $-SO_2$-, $-C(O)-(C_1$-$C_4)$ alkyl-, $-(C_1$-$C_4)$ alkyl-C(O)-, -NH-, or $-N(C_1$-$C_4)$ alkyl-.

In yet another aspect, the invention provides compounds of formula II-15, i.e., compounds of formula II-10, II-11, or 11-12 wherein L is $-C_1-C_6$ alkenyl- or $-C_1-C_6$ alkynyl-, each of which.

In still yet another aspect, the invention provides compounds of formula II-16, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)alkyl-C(O)NR_9-$, $-(C_1-C_4)alkyl-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)alkyl-$, or $-N(R_9)C(O)-(C_1-C_4)alkyl-$, wherein

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl(C_1-C_4)alkyl, or naphthylalkyl, wherein each of the preceding aryl groups is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl(C_1-C_6)alkyl$, CF_3, or OCF_3.

In another aspect, the invention provides compounds of formula II-17, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is $-N(R_9)SO_2-$, or $-SO_2N(R_9)-$, and wherein R_9 is as defined for formula II-16.

In yet another aspect, the invention provides compounds of formula II-18, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is $-N(R_9)-$, $-N(R_9)-(C_1-C_4)alkyl-$, or $-(C_1-C_4)alkyl-N(R_9)-$, and wherein R_9 is as defined for formula II-16.

In still another aspect, the invention provides compounds of formula II-19, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is $-O-(C_1-C_6)alkyl-$, or $-(C_1-C_6)alkyl-O-$.

In another aspect, the invention provides compounds of formula II-20, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is a bond, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, or $-N(R_9)-$, and wherein R_9 is as defined for formula II-16.

In yet another aspect, the invention provides compounds of formula II-21, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, or II-20, wherein R_2 is phenyl, phenyl(C_1-C_4)alkyl (in another aspect, benzyl), wherein the phenyl portion of each of the preceding is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, CF_3 or OCF_3.

In yet another aspect, the invention provides compounds of formula II-22, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, or II-20, wherein R_2 is phenyl or benzyl.

In yet another aspect, the invention provides compounds of formula II-23, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, or II-20, wherein R_2 is C_1-C_6 alkyl, $-(C_1-C_4)$ alkyl-pyridinyl, or (C_1-C_4) hydroxyalkyl.

In still another aspect, the invention provides compounds of formula II-24, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, or II-23 wherein the A ring is phenyl or naphthyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2,

$NH(C_1-C_6)alkyl$, or $N(C_1-C_6)alkyl(C_1-C_6)alkyl$. In another aspect, the A-ring is unsubstituted.

In still another aspect, the invention provides compounds of formula II-25, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, or II-23 wherein the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, pyrimidyl, imidazolyl, isothiazolyl, or pyrrolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)alkyl$, or $N(C_1-C_6)alkyl(C_1-C_6)alkyl$. In another aspect, the A-ring is unsubstituted.

In still another aspect, the invention provides compounds of formula II-26, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, or II-23 wherein the A ring is benzofuranyl, dibenzofuranyl, quinazolinyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)alkyl$, or $N(C_1-C_6)alkyl(C_1-C_6)alkyl$. In another aspect, the A-ring is unsubstituted.

In still another aspect, the invention provides compounds of formula II-27, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, or piperazinyl,

wherein the aforementioned cyclic groups are optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In still another aspect, the invention provides compounds of formula II-28, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or phenyl.

In still another aspect, the invention provides compounds of formula II-29, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is -phenyl-carbonyl-phenyl, -phenyl-(C_1-C_4)alkyl-phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-

pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-pyridyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl(C_1-C_6)alkyl, or $-SO_2$-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In still another aspect, the invention provides compounds of formula II-30, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is -phenyl-carbonyl-phenyl, -phenyl-(C_1-C_4)alkyl-phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-pyridyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, or 3 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or phenyl.

In still another aspect, the invention provides compounds of formula II-31, i.e., compounds of formula II-9, II-10, II-

11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is C_1-C_6 alkyl, halogen, CF_3, OCF_3, or C_1-C_6 alkoxycarbonyl.

In still another aspect, the invention provides compounds of formula II-32, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is H.

In still another aspect, the invention provides compounds of formula II-33, i.e., compounds of formula II-27 or II-29, wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_4 alkanoyl, phenyl(C_1-C_4)alkanoyl, C_1-C_4 alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, wherein each of the preceding cyclic groups is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

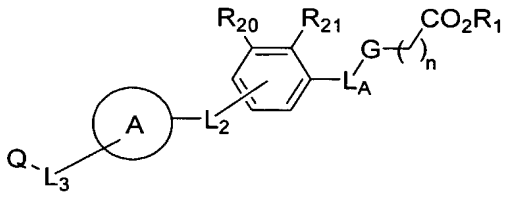
In still another aspect, the invention provides compounds of formula II-34, i.e., compounds of formula II-27 or II-29, wherein R_6 and R_7 are independently H, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_4)alkyl, -C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, or -SO_2-phenyl, wherein each of the preceding cyclic groups is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-35, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-

20, II-21, II-22, II-23, II-24, II-25, II-26, II-27, II-28, II-29, II-30, II-31, II-32, wherein Z is absent or H.

In still another aspect, the invention provides compounds of formula II-36, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, II-26, II-27, II-28, II-29, II-30, II-31, II-32, wherein Z is phenyl, which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NO_2. In another aspect, the phenyl group is monosubstituted. In yet another aspect, the phenyl group is unsubstituted.

Preferred compounds or salts of formula II-9 include compounds of formula III,



III

Wherein

G is a bond or C(H)(R_2);

R_1 is H, C_1-C_6 alkyl, benzyl, or allyl;

R_2 is H, phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, -CH_2-pyridyl, or (C_1-C_4) hydroxyalkyl, wherein the phenyl and pyridyl portions are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

L_A is -C_2-C_6 alkenyl-, optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy; and

R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, NH-phenyl, NHphenylalkyl, $N(C_1$-$C_4)$alkyl-phenyl, $-NHSO_2$-phenyl, $-N(C_1$-C_4alkyl$)SO_2$phenyl, or $-N(C_1$-C_4alkyl$)$phenyl$(C_1$-$C_6)$alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy.

Preferred compounds of formula III include compounds wherein L_2 is in a meta position on the phenylene ring relative to L_A.

Preferred compounds of formula III further include compounds wherein L_2 is in the para position on the phenylene ring relative to L_A.

Preferred compounds of formula III include compounds of formula III-1, i.e., compounds wherein

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dibenzofuranyl, dihydropyrazolyl, benzofuranyl, pyrimidyl, quinazolinyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-$(C_1$-$C_4)$alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

Preferred compounds of formula III-1 include compounds of formula III-2, i.e., compounds wherein

R_1 is H;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenylalkyl, naphthyl-CH_2-, or anthracenyl-CH_2-, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, C(O);

R_2 is phenyl, phenyl(C_1-C_4)alkyl, -CH_2-pyridyl, or C_1-C_6 alkyl wherein the phenyl and the pyridyl portions are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In another aspect, the invention provides compounds of formula III-2-a, i.e., compounds of formula III-2 wherein L_3 is -(C_1-C_4)alkyl-O-, or -O-(C_1-C_4)alkyl.

In yet another aspect, the invention provides compounds of formula III-2-b, i.e., compounds of formula III-2 wherein L_3 is -(C_1-C_4) alkyl-, or C(O). In one aspect, L_3 is C(O). In another aspect, L_3 is -(C_1-C_3) alkyl-.

In yet another aspect, the invention provides compounds of formula III-2-c, i.e., compounds of formula III-2, III-2-a or III-2-b wherein R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl. In another aspect, at least one of R_{20} and R_{21} are H.

In yet another aspect, the invention provides compounds of formula III-2-d, i.e., compounds of formula III-2, III-2-a or III-2-b wherein R_{20} and R_{21}, are independently selected from H, NH-phenyl, NHbenzyl, N(C_1-C_4)alkyl-phenyl, -NHSO$_2$-phenyl, -N(C_1-C_4 alkyl)SO$_2$phenyl, or -N(C_1-C_4 alkyl)phenyl(C_1-C_6)alkyl, wherein each of the preceding phenyl groups are optionally substituted with 1, 2, 3, or 4 groups (in another aspect, 1, 2, or 3 groups) that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3. In another aspect, at least one of R_{20} and R_{21} are H.

In yet another aspect, the invention provides compounds of formula III-2-e, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, or III-2-d wherein R_2 is phenyl, or phenyl(C_1-C_4)alkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3.

In yet another aspect, the invention provides compounds of formula III-2-f, i.e., compounds of formula III-2-e wherein R_2 is phenyl, which is optionally substituted with a total of 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3. In another aspect, the phenyl is unsubstituted.

In still another aspect, the invention provides compounds of formula III-2-g, i.e., compounds of formula III-2-e wherein R_2 is phenyl(C_1-C_4)alkyl, which is optionally substituted with a total of 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3. In a more preferred aspect, R_2 is benzyl, which is optionally substituted as above. In still another aspect, the benzyl is unsubstituted.

In yet another aspect, the invention provides compounds of formula III-2-h, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, or III-2-d wherein R_2 is -CH_2-pyridyl, or C_1-C_6 alkyl wherein the pyridyl group is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3. In another aspect, R_2 is unsubstituted -CH_2-pyridyl. In still another aspect, R_2 is C_1-C_6 alkyl. In yet still another aspect, R_2 is C_1-C_4 alkyl.

In still yet another aspect, the invention provides compounds of formula III-2-i, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, or III-2-h, wherein Q is H, phenyl, naphthyl, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In yet another aspect, the invention provides compounds of formula III-2-j, i.e., compounds of formula III-2-i, wherein Q is phenyl, naphthyl, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, benzyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, or -SO_2-phenyl.

In still yet another aspect, the invention provides compounds of formula III-2-k, i.e., compounds of formula III-2-i or III-2-j, wherein Q is phenyl or naphthyl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl. In another aspect, Q is phenyl, which is optionally substituted as described above.

In still yet another aspect, the invention provides compounds of formula III-2-l, i.e., compounds of formula III-2-i or III-2-j, wherein Q is pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, benzyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, or -SO_2-phenyl. In another aspect, Q is pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, each of which is unsubstituted.

In yet another aspect, the invention provides compounds of formula III-2-m, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, or III-2-h, wherein Q is -phenyl-pyridyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_4)alkyl, N(C_1-C_4)alkyl(C_1-C_4)alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-n, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A ring is phenyl, or naphthyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl. In another aspect, the

A ring is phenyl, which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the A ring is substituted with at least one group. In still another aspect, the A ring is unsubstituted.

In still another aspect, the invention provides compounds of formula III-2-o, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, or pyrimidyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl.

In another aspect, the invention provides compounds of formula III-2-p, i.e., compounds of formula III-2-o wherein the A ring is thiazolyl, which is optionally substituted with one group that is halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the thiazolyl ring is unsubstituted.

In another aspect, the invention provides compounds of formula III-2-q, i.e., compounds of formula III-2-o wherein the A ring is pyrazolyl, which is optionally substituted with one group that is halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the pyrazolyl ring is unsubstituted.

In still another aspect, the invention provides compounds of formula III-2-r, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A

ring is dibenzofuranyl, benzofuranyl, quinazolinyl, or benzo[b]thienyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl.

In still another aspect, the invention provides compounds of formula III-2-s, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A ring is dibenzofuranyl or benzofuranyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the A ring is dibenzofuranyl, which is optionally monosubstituted with a group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_4)$alkyl, or $N(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkyl. In yet another aspect, the dibenzofuranyl group is unsubstituted.

In yet another aspect, the invention provides compounds of formula III-2-t, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is a bond.

In another aspect, the invention provides compounds of formula III-2-u, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is $-C(O)NR_9-$, $-N(R_9)C(O)-$, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl$(C_1$-$C_4)$alkyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups that are

independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-v, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl$(C_1$-$C_4)$alkyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-w, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is $-N(R_9)-$, $-N(R_9)-(C_1$-$C_4)$alkyl-, or $-(C_1$-$C_4)$alkyl-$N(R_9)-$, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl$(C_1$-$C_4)$alkyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-x, i.e., compounds of formula III-2-u, III-2-v, or III-2-w, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, benzyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups (in another aspect, the aryl groups are optionally substituted with 1 or 2 groups) that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_4)$alkyl, $N(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkyl, CF_3 or OCF_3. In

another aspect, the phenyl groups are not substituted. In still another aspect, the phenyl groups are monosubstituted.

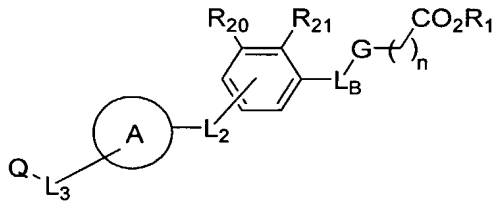
Preferred compounds of formula III-2 include compounds of formula III-3, i.e., compounds wherein

L_3 is a bond; R_2 is phenyl, benzyl, phenethyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

Q is H, or phenyl, optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; and

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dihydropyrazolyl, quinazolinyl, and benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl.

Other preferred compounds or salts of formula II-8 include compounds of formula IV



IV

wherein

G is a bond or C(H)(R_2);

R_1 is H or methyl (preferably H);

R_2 is phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, or (C_1-C_4) hydroxyalkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are

independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; and

L_B is -C_2-C_6 alkenyl-, optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy.

Preferred compounds of formula IV include compounds wherein L_2 is in a meta position on the phenylene ring relative to L_B.

Preferred compounds of formula III further include compounds wherein L_2 is in the para position on the phenylene ring relative to L_B.

Preferred compounds of formula IV include compounds of formula IV-1, i.e., compounds wherein,

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, quinolinyl, dihydropyrazolyl, benzofuranyl, pyrimidyl, quinazolinyl, furanyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, CF_3, OCF_3, CN, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl; and

R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, -NHC(O)phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -NHSO_2-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy.

Preferred compounds of formula IV-1 include compounds of formula IV-2, i.e., compounds wherein,

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)$alkyl-, or $-(C_1-C_4)$alkyl-$N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenylalkyl, naphthyl-CH_2-, or anthracenyl-CH_2-, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, $-(C_1-C_4)$alkyl-O-, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$ alkyl-, C(O);

R_2 is phenyl, phenyl(C_1-C_4)alkyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, CF_3, or OCF_3;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

Preferred compounds of formula IV-2 include compounds of formula IV-3, i.e., compounds wherein, Q is H or phenyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3.

Preferred compounds of formula IV-3 include compounds of formula IV-4, i.e., compounds wherein

L_3 is a bond;

R_1 is H or C_1-C_4 alkyl; and

R_2 is phenyl, benzyl, phenethyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3.

In another aspect, the invention provides compounds of formula IV-5, i.e., compounds of formula IV, IV-4, IV-3, VI-2, or IV-1, wherein at least one of R_{20} and R_{21} is H.

Other compounds of formula IV-4 include compounds of formula IV-6, i.e., compounds wherein both R_{20} and R_{21} are H.

Other compounds of formula IV-5 include those wherein R_{21} is H and R_{20} is -N(H or C_1-C_4 alkyl)phenyl or -N(H or C_1-C_4 alkyl)SO_2-phenyl wherein the phenyl is optionally substituted with C_1-C_6 alkyl. More preferably, the phenyl is substituted with C_2-C_5 alkyl. Even more preferably with n-butyl. Still more preferably, it is substituted at the four position.

Preferred compounds of Formula I include those where the A ring is phenyl substituted as specified above. In this preferred aspect, the phenyl is substituted with at least one aryl or heteroaryl group, e.g., phenyl or benzofuryl, where the aryl or heteroaryl group is optionally mono-, di- or trisubstituted as specified above.

A preferred "A ring-L_3-Q" group within Formula I is biphenyl, i.e., where the A ring is phenyl, L_3 is a bond, and Q is phenyl that is optionally substituted as specified above.

Other preferred compounds of Formula I include those where the A ring is thiazolyl, preferably 2- or 4-thiazolyl, and more preferably a 2- or 4-thiazolyl group substituted with at least one phenyl or pyridinyl group (from either Z or Q), where the phenyl and pyridinyl groups are optionally mono-, di- or

trisubstituted as specified above. Particularly preferred compounds of this aspect include those where the A ring is 2- or 4-thiazolyl disubstituted as specified above.

Other preferred compounds of Formula I include those where the A ring is pyrazolyl, preferably 1-pyrazolyl, and more preferably a 1-pyrazolyl group substituted with at least one phenyl or pyridinyl group (from either Z or Q), where the phenyl and pyridinyl groups are optionally mono-, di- or trisubstituted as specified above. In this aspect, the at least one phenyl or pyridinyl group is preferably in the 3- or 5-position of the pyrazole A ring. Particularly preferred compounds include those where the A ring is pyrazolyl disubstituted in the 3- and 5- or 3- and 4-positions of the pyrazole A ring.

Still other preferred compounds of Formula I are those where L_2 is -NHC(O)- or -N[$(C_1$-$C_6)$alkyl]C(O)-, more preferably -NHC(O)-.

Still other preferred compounds of Formula I are those where L_2 is -C(O)-. Other preferred compounds of Formula I include those where L_2 is -$S(O)_2$N[$(C_1$-$C_6)$alkyl]-.

Another preferred L_2 group is -[$(C_1$-$C_3)$alkylene]N(R_9)-. Preferably R_9 in this aspect is -SO_2-phenyl where the phenyl is optionally substituted as specified above. More preferably, the phenyl groups within the scope of R_9 are substituted with haloalkyl or halogen and even more preferably disubstituted where at least one of the substituents is haloalkyl or halogen.

Other preferred compounds of Formula I are those where n is 0. In this aspect, more preferred compounds are those where R_2 is phenyl or benzyl, most preferably benzyl. In certain aspects R_2 is benzyl optionally substituted with one or two C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, or trifluoromethyl.

In another aspect, the invention provides a method of treating diabetes, comprising administering to a patient in

need of such treatment a pharmaceutically acceptable amount of a compounds of formula I.

In another aspect, the invention encompasses a method of treating diabetes comprising administering to a patient in need thereof, a pharmaceutically acceptable amount of a compound or salt of formula I or a pharmaceutical composition comprising a compound or salt of formula I.

In another aspect, the invention encompasses a method of inhibiting TPT-1B comprising administering to a patient in need thereof, a pharmaceutically acceptable amount of a compound or salt of formula I or a pharmaceutical composition comprising a compound or salt of formula I.

In another aspect, the invention encompasses a method of treating cancer or neurodegenerative diseases comprising administering to a patient in need thereof, a pharmaceutically acceptable amount of a compound or salt of formula I or a pharmaceutical composition comprising a compound or salt of formula I.

Illustrative compounds of the invention include the following, which were named using ChemDraw v. 6.02, which is sold by Cambridgesoft.com in Cambridge, MA.

As noted above, compounds of the invention bind to and preferably, inhibit PTP-1B. As a result, compounds of the invention are useful in the treatment of various diseases, including controlling or treating Type 2 diabetes, improving glucose tolerance, and in improving insulin sensitivity in patients in need thereof. Compounds or their pharmaceutically acceptable salts are also useful in treating or controlling other PTP-1B mediated diseases, such as the treatment of cancer, neurodegenerative diseases and the like.

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached to the parent molecular moiety through an oxygen bridge. Examples of alkoxy groups include, for example, methoxy, ethoxy, propoxy, isopropoxy and hexyloxy.

As used herein, the term "alkyl" includes those alkyl groups of a designed number of carbon atoms. Alkyl groups may be straight, or branched. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, and the like.

The term "aryl" refers to an aromatic hydrocarbon ring system containing at least one aromatic ring. The aromatic ring may optionally be fused or otherwise attached to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. Examples of aryl groups include, for example, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene and biphenyl. Preferred examples of aryl groups include phenyl, naphthyl, and anthracenyl. More preferred aryl groups are phenyl and naphthyl. Most preferred is phenyl.

The term "cycloalkyl" refers to a C_3-C_{10} cyclic hydrocarbon having one ring or two or three fused rings. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantanyl, and cyclooctyl.

The terms "halogen" or "halo" indicate fluorine, chlorine, bromine, and/or iodine.

The term "heterocycloalkyl," refers to a ring or ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur, wherein said heteroatom is in a non-aromatic ring. The heterocycloalkyl ring is optionally fused to or otherwise attached to other heterocycloalkyl rings and/or non-aromatic hydrocarbon rings and/or phenyl rings. Preferred heterocycloalkyl groups have from 3 to 7 members. Examples of heterocycloalkyl groups include, for example, 1,2,3,4-tetrahydroisoquinolinyl, 3,4-tetrahydroisoquinolin-1-

yl, piperazinyl, morpholinyl, piperidinyl, tetrahydrofuranyl, pyrrolidinyl, pyridinonyl, and pyrazolyl. Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 3,4-dihydroisoquinolin-1-yl, pyridinonyl, dihydropyrrolidinyl, and pyrrolidinonyl.

The term "heteroaryl" refers to an aromatic ring containing at least one heteroatom selected from nitrogen, oxygen, and sulfur. The heteroaryl ring may be fused or otherwise attached to one or more heteroaryl rings, aromatic or non-aromatic hydrocarbon rings or heterocycloalkyl rings. Examples of heteroaryl groups include, for example, pyridine, furan, thienyl, 5,6,7,8-tetrahydroisoquinoline and pyrimidine. Preferred examples of heteroaryl groups include thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, and benzopyrazolyl.

The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates, chiral non-racemic or diastereomers. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent; chromatography, using, for example a chiral HPLC column; or derivatizing the racemic mixture with a resolving reagent to generate diastereomers, separating the diastereomers via chromatography, and removing the resolving agent to generate the original compound in enantiomerically enriched form. Any

of the above procedures can be repeated to increase the enantiomeric purity of a compound.

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended that the compounds include the cis, trans, Z- and E- configurations. Likewise, all tautomeric forms are also intended to be included.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of

tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques. In some cases such coatings may be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Formulations for oral use may also be presented as lozenges.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide

with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a

mixture of at least one emulsifier with a fat, an oil, or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w. For

therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient. The daily dose can be administered in one to four doses per day. In the case of skin

conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It may be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to the feed or drinking water. Preferred non-human animals include domesticated animals.

As noted above, the invention also provides methods and compositions for combination therapy of Type I and Type II diabetes. In one such aspect, the invention provides methods of using compounds of formula I in combination with one or more angiotensin converting enzyme (ACE) inhibitors for improving the cardiovascular risk profile in patients experiencing or subject to Syndrome X or type II diabetes (non-insulin-dependent diabetes mellitus), preferably in human type II diabetics. These methods may also be characterized as the reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic.

These methods include the reduction of hyperlipidemia in a patients experiencing or subject to Syndrome X or type II diabetes. These methods include methods lowering low density lipoprotein (LDL) blood levels and to increase high density lipoprotein (HDL) blood levels. The methods herein may further

be characterized as useful for inhibiting, preventing or reducing atherosclerosis in a type II diabetics, or for reducing the risk factors thereof.

These methods also include the lowering of free fatty acid blood levels and triglyceride levels in type II diabetics.

Among the ACE inhibitors which may be utilized with the invention described herein are quinapril, ramipril, verapamil, captopril, diltiazem, clonidine, hydrochlorthiazide, benazepril, prazosin, fosinopril, lisinopril, atenolol, enalapril, perindropril, perindropril tert-butylamine, trandolapril and moexipril, or a pharmaceutically acceptable salt form of one or more of these compounds.

The invention also provides methods of using PTPase inhibitors of formula I for improving the cardiovascular or cerebrovascular risk profile in patients experiencing or subject to type II diabetes (non-insulin-dependent diabetes mellitus), preferably in human type II diabetics or a patient experiencing or subject to Syndrome X. These methods may also be characterized as the reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic or a patient experiencing or subject to Syndrome X.

The invention also provides methods of using a pharmacological combination of one or more PTPase inhibiting agents, one or more biguanide agents, and, optionally one or more sulfonlylurea agents for treatment of type II diabetes or Syndrome X in a patient in need of such treatment. Also provided are methodS of using these agents to treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia in a patient in need thereof. Further included in this invention is a method of modulating blood glucose levels in a patient in need thereof.

Each of these methods comprises administering to a patient in need thereof pharmaceutically effective amounts of:

a) a PTPase inhibiting agent of formula I; and

b) a biguanide agent; and

c) optionally, a sulfonylurea agent.

Biguanide agents useful with this invention include metformin and its pharmaceutically acceptable salt forms. Sulfonylurea agents useful for the methods and combinations of this invention may be selected from the group of glyburide, glyburide, glipizide, glimepiride, chlorpropamide, tolbutamide, or tolazamide, or a pharmaceutically acceptable salt form of these agents.

This invention also provides pharmaceutical compositions and methods of using PTPase inhibitors of formula I in combination with one or more alpha-glucosidase inhibitors, such as miglitol or acarbose, for improving the cardiovascular risk profile in patients experiencing or subject to Syndrome X or type II diabetes (non-insulin-dependent diabetes mellitus), preferably in human type II diabetics. These methods may also be characterized as the reduction of risk factors for heart disease, stroke or heart attack in a patient in such need.

These methods include the reduction of hyperlipidemia in type II diabetics, including methods in type II diabetics for lowering low density lipoprotein (LDL) blood levels and to increase high density lipoprotein (HDL) blood levels. The methods herein may further be characterized as useful for inhibiting, preventing or reducing atherosclerosis in a type II diabetic or a patient experiencing or subject to Syndrome X, or the risk factors of either.

These methods also include the lowering free fatty acid blood levels and triglyceride levels in type II diabetics, or a patient experiencing or subject to Syndrome X.

Among the alpha-glucosidase inhibitors which may be utilized with the invention described herein are miglitol or acarbose, or a pharmaceutically acceptable salt form of one or more of these compounds.

This invention further provides methods for using a PTPase inhibitor of the invention and a sulfonylurea agent for the management of Syndrome X or type 2 diabetes and for improving the cardiovascular risk profile in patients experiencing or subject to those maladies. These methods may also be characterized as the reduction of risk factors in such patients for heart disease, stroke or heart attack in a type II diabetic. Such methods include the reduction of hyperlipidemia in a patients experiencing or subject to Syndrome X or type II diabetes and include methods for lowering low density lipoprotein (LDL) blood levels, high density lipoprotein (HDL) blood levels, and overall blood lipoprotein levels. The methods herein may further be characterized as inhibiting, preventing or reducing atherosclerosis in patients subject to or experiencing Syndrome X or type II diabetes, or the risk factors thereof. Such methods further include the lowering of free fatty acid blood levels and triglyceride levels in such patients.

Representative sulfonylurea agents include glipizide, glyburide (glibenclamide), chlorpropamide, tolbutamide, tolazamide and glimepriride, or the pharmaceutically acceptable salt forms thereof.

In addition, the invention provides combinations of a PTPase inhibitor of the invention and at least one thiazolidinedione agents. Such combinations are useful for treatment, inhibition or maintenance of Syndrome X or type II diabetes in patients in need of such treatment. Accordingly, methods of using such combinations are provided by the invention. Thus, the invention provides methods of using these agents to treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia in patients in need thereof. Further included in this invention are methods of modulating blood glucose levels in a patient in need thereof.

Each of these methods comprises administering to a patient in need thereof pharmaceutically effective amounts of:

a) a thiazolidinedione agent, such as selected from the group of pioglitizone and rosiglitazone, or a pharmaceutically acceptable salt form of these agents; and

b) a compound of formula I.

The invention also provides pharmaceutical compositions and methods of using PTPase inhibitors in combination with one or more antilipemic agents. Such methods and compositions are useful for improving the cardiovascular risk profile in patients experiencing or subject to type II diabetes (non-insulin-dependent diabetes mellitus), preferably in type II diabetics or Syndrome X. These methods also include reducing the risk factors for heart disease, stroke or heart attack in a type II diabetic or a patient experiencing or subject to Syndrome X. Such methods further include the reduction of hyperlipidemia in type II diabetics, including such methods in type II diabetics for lowering low density lipoprotein (LDL) blood levels and to increase high density lipoprotein (HDL) blood levels. These compositions and methods are also useful for inhibiting, preventing or reducing atherosclerosis in a type II diabetic or a patient experiencing or subject to Syndrome X, or the risk factors thereof. In this aspect, the compositions and methods are useful for lowering of free fatty acid blood levels and triglyceride levels in type II diabetics, or patients experiencing or subject to Syndrome X.

Representative antilipemic or agents, also known as antihyperlipidemic agents, suitable for use in the invention are bile acid sequestrants, fibric acid derivatives, HMG-CoA reductase inhibitors and nicotinic acid compounds. Bile acid sequestrant agents useful with this invention include colestipol and colesevelam, and their pharmaceutically acceptable salt forms. Fibric acid derivatives which may be used with the present invention include clifofibrate,

gemfibrozil and fenofibrate. HMG-CoA reductase inhibitors, also known as statins, useful with this invention include cerivastatin, fluvastatin, atorvastatin, lovastatin, pravastatin and simvastatin, or the pharmaceutically acceptable salt forms thereof. Niacin is an example of a nicotinic acid compound which may be used with the methods of this invention. Also useful are lipase inhibiting agents, such as orlistat.

This invention also provides pharmaceutical compositions that are a combination of a compound of Formula I and an aldose reductase inhibitor (ARI). Such combinations are useful in methods for treating, inhibiting or preventing type II diabetes, or its related and associated symptoms, disorders and maladies. These methods comprise administering to a patient in need of such therapy a pharmaceutically effective amount of a composition comprising a combination of pharmaceutically effective amounts of a compound of formula I and an ARI. These compositions and methods are useful for the treatment, prevention or inhibition of diabetic neuropathy, diabetic nephropathy, retinopathy, keratopathy, diabetic uveitis, cataracts.

Representative suitable ARIs are disclosed in U.S. Patent Nos. 6,420,426 and 6,214,991.

Combinations of the compounds of Formula I and an ARI are also useful for inhibition or reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic. Therefore, in this aspect the invention is useful for reducing hyperlipidemia and/or low density lipoprotein (LDL) blood levels in type II diabetics. Also included in this aspect are methods for inhibiting, preventing or reducing atherosclerosis or the risk factors thereof in type II diabetics. This aspect includes lowering of free fatty acid blood levels and triglyceride levels.

This invention also provides methods of using a compound of formula I and insulin(s) for the management of type I or

type II diabetes. Accordingly, the invention provides for combination therapy, i.e., where a compound of Formula I is administered in combination with insulin. Such combination therapy encompasses simultaneous or sequential administration of the compound of Formula I and insulin. The insulins useful in this aspect include both naturally occurring and synthetic insulins.

Insulins useful with the methods and combinations of this invention include rapid acting insulins, intermediate acting insulins, long acting insulins and combinations of intermediate and rapid acting insulins.

Rapid acting commercially available insulin products include HUMALOG® Brand Lispro Injection (rDNA origin); HUMULIN® Regular Human Injection, USP [rDNA origin]; HUMULIN® Regular U-500 Concentrated Human Injection, USP [rDNA origin]; REGULAR ILETIN® II (insulin injection, USP, purified pork) available from Eli Lilly and Co.; and the NOVALIN® Human Insulin Injection and VENOSULIN® BR Buffered Regular Human Injection, each available from Novo Nordisk Pharmaceuticals.

Commercially available intermediate acting insulins useful with this invention include, but are not limited to, the HUMULIN® L brand LENTE® human insulin [rDNA origin] zinc suspension, HUMULIN® N NPH human insulin [rDNA origin] isophane suspension, LENTE® ILETIN.RTM. II insulin zinc suspension, USP, purified pork, and NPH ILETIN® II isophane insulin suspension, USP, purified pork, available from Eli Lilly and Company, LANTUS® insulin glargine [rDNA origin] injection, available from Aventis Pharmaceuticals, and the NOVOLIN L Lente® human insulin zinc suspension (recombinant DNA origin), and NOVOLIN® N NPH human insulin isophane suspension (recombinant DNA origin) products available from Novo Nordisk Pharmaceuticals, Inc, Princeton N.J.

Also useful with the methods and formulations of this invention are intermediate and rapid acting insulin

combinations, such as the HUMALOG® Mix 75/25 (75% Insulin Lispro Protamine Suspension and 25% Insulin Lispro Injection), HUMULIN® 50/50 (50% Human Insulin Isophane Suspension and 50% Human Insulin Injection) and HUMULIN® 70/30 (70% Human Insulin Isophane Suspension and 30% Human Insulin Injection), each available from Eli Lilly and Company. Also useful are the NOVALIN® 70/30 (70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection) line of combination products available from Novo Nordisk Pharmaceuticals.

A commercially available long acting insulin for use with this invention is the HUMULIN® U Ultralente® human insulin [rDNA origin] extended zinc suspension, available from Eli Lilly and Company.

Also useful in the methods of this invention are inhaled insulin products, such as the EXUBERA® inhaled insulin product developed by Pfizer Inc. and Aventis SA.

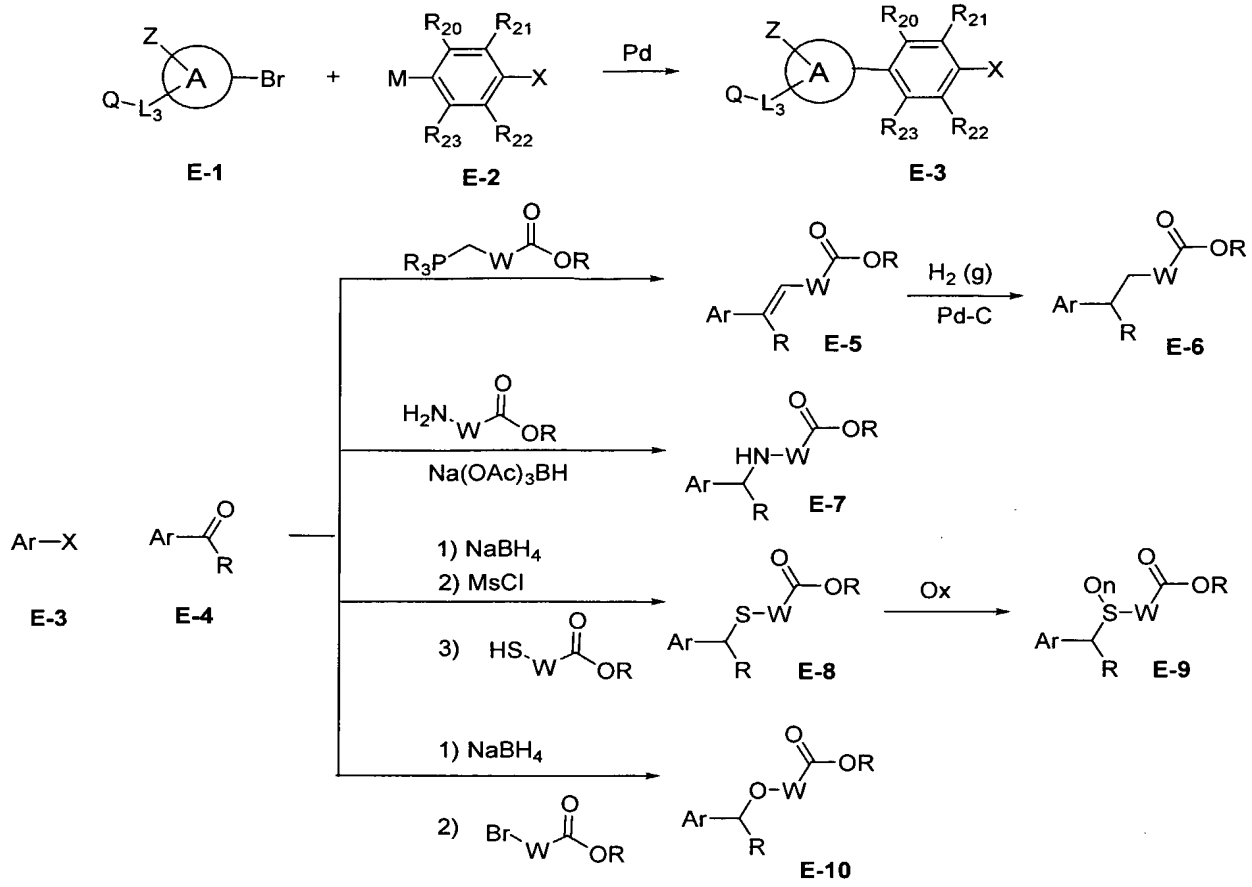
Each of these insulin products can be administered as directed by a medical professional using administrations, dosages and regimens known in the art, such as those published for each product in the Physicians' Desk Reference, 55 Edition, 2001, published by Medical Economics Company, Inc. at Montvale, N.J., the relevant sections of which are incorporated herein by reference. In this aspect, the invention includes, for example, methods for improving the cardiovascular and cerebrovascular risk profiles in patients experiencing or subject to type I or type II diabetes (non-insulin-dependent diabetes mellitus), preferably in human type II diabetics. These methods may also be characterized as the inhibition or reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic.

The compounds of the present invention may be prepared by use of known chemical reactions and procedures. Representative methods for synthesizing compounds of the invention are presented below. It is understood that the nature of the

substituents required for the desired target compound often determines the preferred method of synthesis. All variable groups of these methods are as described in the generic description if they are not specifically defined below.

Methods of Preparation

Compounds with a variety of L_1 linkers (Formula I) can be prepared using the chemistry described in general scheme E. Here aryl or heteroaryl bromide E-1 is coupled to intermediate E-2 containing a functional group X that can be modified to provide the desired L_1-CO_2R substituent. The initial coupling reaction between intermediates E-1 and E-2 can often be carried out using a transition metal coupling reaction. Some of the most useful reactions of this type include the Suzuki, Stille and Negishi reactions. Alternatively, for some examples, it may be more convenient to reverse the coupling functional groups such that metal-M is on the E-1 intermediate and the halogen, preferably Br or I, is on the E-2 intermediate. A variety of X substituents may be useful for preparing compounds with a specific L_1-CO_2R group. Some useful X substituents include sulfonamides, acids, esters, aldehydes, ketones, amides, nitro groups, anilino groups, hydroxyl groups, sulfides and halides. Some examples of target compounds prepared from intermediate E-3 with X equal to aldehyde or ketone are illustrated in scheme E.



Scheme E

Treatment of carbonyl compound E-4 with a Wittig type reagent provides the unsaturated derivative E-5. If the saturated compound E-6 is required, simple hydrogenation with, for example, palladium on carbon can be used. In some cases the carboxylic acid moiety (R = H) may need to be protected as an ester to facilitate the reactions in the scheme. Carbonyl compound E-4 can also be coupled with an amine derivative using a reducing agent like sodium triacetoxyborohydride in a reductive amination reaction to give the corresponding amine E-7. Reduction of aldehyde or ketone E-4 with sodium borohydride gives the corresponding alcohol. Subsequent conversion of this alcohol to a leaving group such as a mesylate or halide followed be displacement with a nucleophile such as a thiol gives sulfide E-8, which if desired can be oxidized to form the

sulfoxide or sulfone. Similarly, the same mesylate or halogen leaving group can be displaced by other nucleophiles like amines or alcohols to give the corresponding amine and ether linkers. The sodium borohydride reduction product can also be coupled directly to an alkyl halide or substituted phenol using simple alkylation or Mitsunobu conditions respectively.

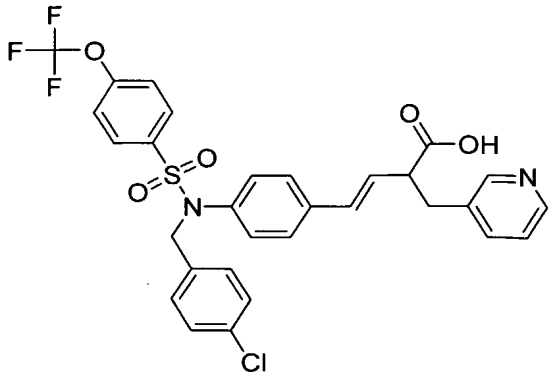
Those having skill in the art will recognize that the starting materials and reaction conditions may be varied, the sequence of the reactions altered, and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, the need for such protecting groups as well as the conditions necessary to attach and remove such groups will be apparent to those skilled in the art of organic synthesis.

The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference in their entirety.

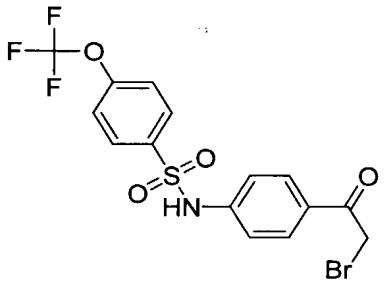
The preparation of the compounds of the present invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. In all cases, unless otherwise specified, the column chromatography is performed using a silica gel solid phase.

Example 3

(3*E*)-4-[4-((4-chlorobenzyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-2-(pyridin-3-ylmethyl)but-3-enoic acid.



Step 1: *N*-[4-(2-Bromoacetyl)-phenyl]-4-trifluoromethoxybenzenesulfonamide

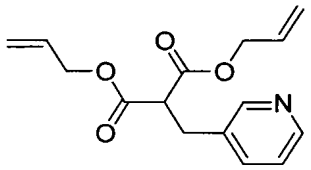


4-Trifluoromethoxybenzenesulfonyl chloride (3.18 g, 2.07 mL, 1.22 mmol) was added to a solution of 4'-aminoacetophenone (1.5 g, 1.11 mmol) and triethylamine (3.1 mL, 2.22 mmol) in anhydrous methylene chloride (50 mL). The reaction was stirred for 16 hours and then poured into water (50 mL), and extracted with diethyl ether (3 x 30 mL). The combined extract was washed with 0.5 N hydrochloric acid (2 x 10 mL), water and finally brine. The ethereal solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The product methyl ketone was used in the subsequent bromination step without further purification.

Phenyltrimethylammonium tribromide (4.68 g, 1.22 mmol) was added to a solution of the methyl ketone (prepared in the previous step) in anhydrous dioxan (50 mL). The reaction eas stirred at room temperature for 3 hours and then poured into water (50 mL), and extracted with diethyl ether (3 x 30 mL). The combined extract was washed with 0water and brine. The ethereal solution was dried over anhydrous $MgSO_4$, filtered and

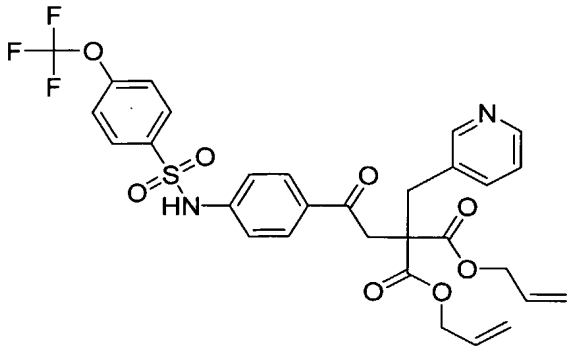
concentrated *in vacuo*. Purification of the product by flash column chromatography, using 20 % ethyl acetate/heptane as eluent, afforded the title compound has a white solid (4.36 g, 89%); 1H NMR ($CDCl_3$, 300 MHz): δ 7.92 (4H, d, J = 8 Hz, Ar-H), 7.38 (2H, d, J = 8 Hz, Ar-H), 7.20 (3H, m, Ar-H, NH), 4.38 (2H, s, CH_2Br).

Step 2: 2-Pyridin-3-ylmethyl-malonic acid diallyl ester



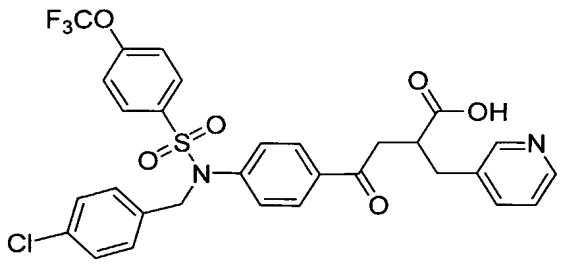
A solution of diallyl malonate (3.0 g, 16.3 mmol) in anhydrous THF (30 mL) was added cautiously to a stirred suspension of sodium hydride (95%, 900 mg, 36 mmol) in anhydrous THF (25 mL). The resulting solution was stirred at room temperature for 1 hr. A solution of 3-(iodomethyl)pyridine hydroiodide (6.24 g, 18 mmol) in anhydrous THF (25 mL) was added dropwise, and the resultant solution was stirred at room temperature for 16-24 hrs (TLC control). The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The combined extract was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Trituration and filtration from MeOH afforded the title compound as a white solid (4.03g, 90%); 1H NMR ($CDCl_3$, 300 MHz): δ 8.48 (2H, m), 7.38 (1H, td, J = 8, 2 Hz, Ar-H), 7.20 (2H, dd, J = 8, 5 Hz), 5.82 (2H, m), 5.26 (4H, m), 4.60 (4H, m), 3.88 (1H, t, J = 7 Hz), 3.21 (2H, d, J = 7 Hz).

Step 3: 2-{2-oxo-2-[4-(4-trifluoromethoxybenzenesulfonylamino]-ethyl}-2-pyridin-3-ylmethyl-malonic acid diallyl ester



A solution of 2-pyridin-3-ylmethyl-malonic acid diallyl ester (1.15g, 4.18 mmol) in anhydrous THF (30 mL) was added to a stirred suspension of sodium hydride (95%, 232 mg, 9.2 mmol) in anhydrous THF (25 mL). The resulting solution was stirred at room temperature for 1 hr. A solution of N-[4-(2-Bromoacetyl)-phenyl]-4-trifluoromethoxy-benzenesulfonamide (2.01 g, 4.6 mmol) in anhydrous THF (25 mL) was added dropwise, and the resultant solution was stirred at 50°C for 5 hrs (TLC control). The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The combined extract was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the product by flash column chromatography, using 20 % ethyl acetate/heptane as eluent, afforded the title compound has a white solid (4.36 g, 89%); 1H NMR ($CDCl_3$, 300 MHz): δ 8.48 (1H, d, J = 3 Hz), 8.20 (1H, s), 7.90 (2H, d, J = 8 Hz), 7.78 (2H, d, J = 8 Hz), 7.42 (1H, d, J = 7 Hz), 7.32 (3H, m), 7.20 (1H, m), 7.12 (2H, d, J = 8 Hz), 5.88 (2H, m), 5.29 (4H, m), 4.62 (4H, s), 3.58 (2H, s), 3.50 (2H, s); ESI-LCMS e/z calcd for $C_{30}H_{27}F_3N_2O_8S$: 632.610, found 633 $(M+H)^+$.

Step 4: 4-{4-[(-Chlorobenzyl)-(4-trifluoromethoxybenzenesulfonyl)-amino]-phenyl}-4-oxo-2-pyridin-3-ylmethyl-butyric acid.



A solution of 2-{2-oxo-2-[4-(4-trifluoromethoxybenzenesulfonylamino]-ethyl}-2-pyridin-3-ylmethyl-malonic acid diallyl ester (1.06g, 1.67 mmol) in anhydrous THF (15 mL) was added to a stirred suspension of sodium hydride (95%, 47 mg, 1.84 mmol) in anhydrous THF (10 mL). The resulting solution was stirred at room temperature for 1 hr. A solution of 4-chlorobenzyl chloride (0.3 g, 1.84 mmol) in anhydrous THF (25 mL) was added dropwise, and the resultant solution was stirred at 50°C for 5 hrs (TLC control). The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The combined extract was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* affording the N-alkylated diallyl ester.

The diallyl ester was redissolved in dioxan (15 mL). *Tetrakis*-(Triphenylphospine)-palladium(0) (5 mg) and triethylamine (0.1 mL) was added to the stirred solution, and then the reaction was heated to 100°C for 30 mins, cooled to room temperature and concentrated *in vacuo*. Purification of the product by flash column chromatography, using 20 % ethyl acetate/heptane as eluent, afforded the step 4 compound as a white solid (846 mg, 80%); Rf 0.30 (10% methanol in dichloromethane)1H NMR (MeOH-d4, 300 MHz): δ 8.42 (1H, s), 8.36 (1H, d, J = 3 Hz), 7.84 (2H, d, J = 8 Hz), 7.76 (3H, m), 7.42 (2H, d, J = 8 Hz), 7.35 (1H, dd, J = 8, 3 Hz), 7.20 (5H, m), 4.82 (2H, s), 3.42 (1H, m), 3.20 (1H, m), 3.02 (2H, m), 2.92 (2H, m); ESI-LCMS e/z calcd for $C_{30}H_{24}ClF_3N_2O_6S$: 633.041, found 633 $[M+H(^{35}Cl)]^+$, 635 $[M+H(^{37}Cl)]^+$.

Step 5:

The title compound is conveniently prepared from the acid generated in step 4 by reducing the ketone, for example with sodium borohydride, and subsequently dehydrating the alcohol to yield the desired alkene.

Example 4

(3*E*)-4-(4-{(4-*tert*-butylbenzyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-2-[3-(trifluoromethyl)benzyl]but-3-enoic acid.

Step 1: 2-(3-Trifluoromethylbenzyl)-malonic acid diallyl ester

2-(3-Trifluoromethylbenzyl)-malonic acid diallyl ester was prepared in analogous fashion to 2-Pyridin-3-ylmethyl-malonic acid diallyl ester, using malonic acid diallyl ester (4.5 g, 24.5 mmol), sodium hydride (95%, 680 mg, 27 mmol) and 3-trifluoromethylbenzyl bromide (6.45 g, 27 mmol), to yield the title compound as a colorless oil (6.87 g, 82%), 1H NMR ($CDCl_3$, 300 MHz): δ 7.56 (2H, d, J = 8 Hz), 7.32 (2H, d, J = 8 Hz), 5.82 (2H, m), 5.24 (4H, m), 4.59 (4H, m), 3.72 (1H, t, J = 7 Hz), 3.31 (2H, d, J = 7 Hz).

Step 2: 2-(2-{4-[(4-*tert*-Butylbenzyl)-(3,4-dichlobenzenesulfonyl)-amino]phenyl}-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester

2-(2-{4-[(4-*tert*-Butylbenzyl)-(3,4-dichlobenzenesulfonyl)-amino]phenyl}-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester was synthesized in similar fashion to that reported previously using *N*-{4-(2-bromoacetyl)phenyl]-3,4-dichlorobenzene-sulfonamide as the second step alkylating reagent, to afford the *N*-alkylated product 2-{2-[4-(3,4-dichlorobenzenesulfonylamino)-phenyl]-2-oxoethyl}-2-(3-trifluoromethyl-benzyl}-malonic acid diallyl ester.

N-Alkylation of this intermediate with 4-*tert*-butylbenzyl bromide, under the conditions reported previously, afforded the N,N-dialkylated product. 1H NMR ($CDCl_3$, 300 MHz): δ 7.73 (1H, d, J = 8 Hz), 7.69 (1H, d, J = 2 Hz), 7.56 (2H, m), 7.47 (1H, m), 7.39 (1H, m), 7.32 (2H, m), 7.26 (4H, m), 7.10 (3H, m), 5.88 (2H, m), 5.26 (4H, m), 4.72 (2H, s), 4.64 (4H, m), 3.58 (2H, s), 3.42 (2H, s), 1.26 (9H, s).

Step 3: 4-{4-[(4-tert-Butylbenzyl)-(3,4-dichlorobenzenesulfonyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid.

The step 3 compound was prepared by saponification and decarboxylation of 2-(2-{4-[(4-*tert*-butylbenzyl)-(3,4-dichlobenzenesulfonyl)-amino]phenyl}-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester. Purification of the product by flash column chromatography, using 5 % methanol in dichloromethane as eluent, afforded the title compound has a beige solid; Rf 0.62 (10% methanol in dichloromethane): 1H NMR ($CDCl_3$, 300 MHz): δ 7.77 (1H, d, J = 8 Hz), 7.66 (2H, m), 7.28 - 7.54 (8H, m), 7.24 (2H, d, J = 9 Hz), 7.10 (2H, d, J = 9 Hz), 4.71 (2H, s), 3.16 - 3.38 (3H, m), 2.93 (2H, m), 1.25 (9H, s); ESI-LCMS e/z calcd for $C_{35}H_{32}Cl_2F_3NO_5S$: 706.606, found 706 $(M+H, {}^{35}Cl, {}^{35}Cl)^+$.

Step 4:

The title compound is conveniently prepared from the acid generated in step 3 by reducing the ketone, for example with sodium borohydride, and subsequently dehydrating the alcohol to yield the desired alkene.

Example 5

(3*E*)-4-{4-[[(3,4-dichlorophenyl)sulfonyl](4-isopropylbenzyl)amino]phenyl}-2-[3-(trifluoromethyl)benzyl]but-3-enoic acid.

Step 1: 2-(2-{4-[(3,4-Dichlorobenzenesulfonyl-(4-isopropylbenzyl)-amino]-phenyl-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester

2-(2-{4-[(3,4-Dichlorobenzenesulfonyl-(4-isopropylbenzyl)-amino]-phenyl-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester was synthesized i via alkylation of 2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester with *N*-{4-(2-bromoacetyl)-phenyl]-3,4-dichlorobenzene-sulfonamide, with subsequent *N*-alkylation of this intermediate with 4-isopropylbenzyl bromide to afford the N,N-dialkylated product. 1H NMR ($CDCl_3$, 300 MHz): δ 7.73 (1H, d, J = 8 Hz), 7.69 (1H, s), 7.56 (2H, m), 7.47 (1H, m), 7.36 (3H, m), 7.26 (4H, m), 7.10 (3H, m), 5.89 (2H, m), 5.30 (4H, m), 4.71 (2H, s), 4.66 (4H, m), 3.56 (2H, s), 3.43 (2H, s), 2.83 (1H, sept, J = 7 Hz), 1.20 (3H, s), 1.18 (3H, s).

Step 2: 4-{4-[(3,4-dichlorobenzenesulfonyl)-(4-isopropylbenzyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid.

The step 2 compound prepared by saponification and decarboxylation of 2-(2-{4-[(3,4-dichlorobenzenesulfonyl-(4-isopropylbenzyl)-amino]-phenyl-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester. Purification of the product by flash column chromatography, using 5 % methanol in dichloromethane as eluent, afforded the title compound has a cream solid; Rf 0.60 (10% methanol in dichloromethane): 1H NMR ($CDCl_3$, 300 MHz): δ 7.76 (1H, d, J = 8 Hz), 7.70 (2H, m), 7.28 - 7.62 (8H, m), 7.24 (2H, m), 7.10 (2H, m), 4.70 (2H, s), 3.34 (1H, m), 3.20 (2H, m), 2.89 (2H, m), 2.81 (1H, sept, J = 7Hz), 1.19 (3H, s), 1.17 (3H, s); ESI-LCMS e/z calcd for $C_{34}H_{30}Cl_2F_3NO_5S$: 692.579, found 692 (M+H, ^{35}Cl, $^{35}Cl)^+$.

Step 3:

The title compound is conveniently prepared from the acid generated in step 2 by reducing the ketone, for example with sodium borohydride, and subsequently dehydrating the alcohol to yield the desired alkene.

Example 8

Method for measuring PTP-1B activity

The test compounds are evaluated for their in vitro inhibitory activity against recombinant human PTP1B with phosphotyrosyl dodecapeptide TRDI(P)YETD(P)Y(P)YRK [SEQ ID NO:1]. This corresponds to the 1142-1153 insulin receptor kinase regulatory domain, phosphorylated on the 1146, 1150 and 1151 tyrosine residues; IR-triphosphopeptide as a source of substrate. Enzyme reaction progression is monitored via the release of inorganic phosphate as detected by the malachite green - ammonium molybdate method for the phosphopeptide.

Preferred compounds of the invention exhibit IC_{50} values of less than 10 μM; more preferred compounds of the invention exhibit IC_{50} values of less than 1 μM. Particularly preferred compounds exhibit IC_{50} values of less than 300 nM.

Example 9

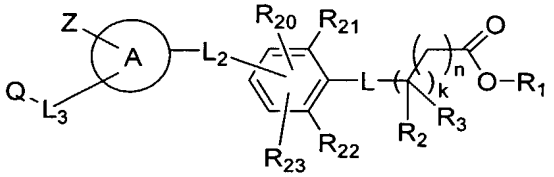
Male Wistar rats are fed a High Fat Diet for at least 4 weeks. Jugular vein and carotid artery cannulations are performed one week prior to the clamp experiment. Test compound is administered p.o. 4 hrs before the clamp and labeled 3-3H-glucose is infused 1 hr prior to calculated endogenous glucose production (EGP). Insulin is infused at a rate of 0.75U/kg/hr raising plasma insulin levels to ~200 mU/ml. To maintain euglycemia (80 mg/dl), unlabeled glucose is infused at a variable rate and adjusted every 10 minutes.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and

exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein

k is 0 or 1;

n is 0, 1, 2, or 3;

each R_1 is independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, or C_3-C_6 alkenyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-heterocycloalkyl, -(C_1-C_4) alkyl-heteroaryl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H or -CO_2R_1,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, arylalkoxy, arylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-aryl, -N(C_1-C_4 alkyl)C(O)aryl, -NHC(O)aryl, NHarylalkyl, NHC(O)-(C_1-C_4) alkyl-aryl, N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-aryl, N(C_1-C_4)alkyl-aryl, -$NHSO_2$-aryl, -N(C_1-C_4alkyl)SO_2aryl, or -N(C_1-C_4alkyl)arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are

independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy;

L is -C_2-C_6 alkenyl-, or -C_2-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy;

L_2 is a bond or -$C(O)NR_9$-, -$N(R_9)C(O)$-, -$(C_1$-$C_4)$alkyl-$C(O)NR_9$-, -$(C_1$-$C_4)$alkyl-$N(R_9)C(O)$-, -$C(O)N(R_9)$-$(C_1$-$C_4)$alkyl-, -$N(R_9)C(O)$ -$(C_1$-$C_4)$alkyl-, -$(C_1$-$C_4)$alkyl-$C(O)N(R_9)$-$(C_1$-$C_4)$alkyl-, -$(C_1$-$C_4)$alkyl-$N(R_9)C(O)$ -$(C_1$-$C_4)$alkyl-, -$N(R_9)SO_2$-, -$SO_2N(R_9)$-, -N(R9)-, -$N(R_9)$-$(C_1$-$C_4)$alkyl-, -O-$(C_1$-$C_6)$alkyl-, -$(C_1$-$C_6)$alkyl-O-, or -$(C_1$-$C_4)$alkyl-$N(R_9)$-,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, -SO_2aryl, arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, -$(C_1$-$C_4)$alkyl-O-, -O-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$ alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, furanyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, pyridyl, quinolinyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, CN, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, cycloalkyl, aryl, -aryl-carbonyl-aryl, -aryl-alkyl-aryl, -aryl-heteroaryl, -aryl-heterocycloalkyl, -heteroaryl, -heteroaryl-alkyl-aryl, -heterocycloalkyl, -aryl-O-aryl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl,

or alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, aryl(C_1-C_6)alkyl, alkanoyl, arylalkanoyl, alkoxycarbonyl, arylalkoxycarbonyl, heteroarylcarbonyl, heteroaryl, heterocycloalkylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, or $-SO_2$-aryl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, haloalkyl or haloalkoxy, and

Z is absent, H, $-NHC(O)$aryl, $-N(C_1$-C_4 alkyl)$C(O)$aryl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, or NO_2, or

Z is $-NHC(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl, $-N(C_1$-$C_4)$alkyl$C(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl;

provided that when L2 is a bond, the A ring is not phenyl.

2. A compound according to claim 1, wherein

R_1 is H, C_1-C_6 alkyl, benzyl, or allyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, $-(C_1$-$C_4)$ alkyl$-C(O)NH_2$, $-(C_1$-$C_4)$ alkyl$-C(O)NH(C_1$-$C_4)$alkyl, $-(C_1$-$C_4)$ alkyl$-C(O)N(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkyl, $-(C_1$-$C_4)$ alkyl$-S(O)_b-(C_1$-$C_4)$ alkyl, (C_1-C_4) hydroxyalkyl, $-(C_1$-$C_4)$ alkyl-pyridinyl, $-(C_1$-$C_4)$ alkyl-piperidinyl, $-(C_1$-$C_4)$ alkyl-pyrrolidinyl, or $-(C_1$-$C_4)$ alkyl-tetrahydrofuranyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the

phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, benzofuranyl, benzothienyl, pyrrolyl, dihydroquinolinyl, dihydroisoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, imidazolyl, adamantanyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, dibenzofuranyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6

alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

3. A compound according to claim 2, wherein

L is -C_2-C_6 alkenyl-, or -C_2-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -C(O)N(R_9)-(C_1-C_4)alkyl-, -N(R_9)C(O) -(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-C(O)N(R_9)-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-N(R_9)C(O) -(C_1-C_4)alkyl-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R9)-, -N(R_9)-(C_1-C_4)alkyl-, -O-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-O-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, anthracenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-

C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -C(O)-; and

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, -NHC(O)-(C_1-C_4) alkyl-phenyl, -N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-phenyl, N(C_1-C_4)alkyl-phenyl, -NHSO_2-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy.

4. A compound according to claim 3, wherein

L is -C_2-C_6 alkenyl- or -C_2-C_6 alkynyl-, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -C(O)N(R_9)-(C_1-C_4)alkyl-, -N(R_9)C(O) -(C_1-C_4)alkyl-,-N(R_9)SO_2-, -SO_2N(R_9)-, -N(R9)-, -N(R_9)-(C_1-C_4)alkyl-, -O-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-O-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -C(O)-;

R_1 is H, C_1-C_6 alkyl, benzyl or allyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-$S(O)_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H;

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, N(C_1-C_4)alkyl-phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-

pyrrolidinyl, -phenyl-piperazinyl, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, adamantanyl, -pyridyl-(C_1-C_4)alkyl-phenyl, imidazolidinyl, dibenzofuranyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

5. A compound according to claim 1, wherein

n is 0, 1, 2, or 3;

R_1 is H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, or C_3-C_6 alkenyl;

R_2 is H, phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4)

alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-pyridinyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, or -(C_1-C_4) alkyl-tetrahydrofuranyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;
wherein b is 0, 1, or 2;

R_3 is H or -CO_2R_1,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, phenylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, -NHC(O)phenyl, NHphenylalkyl, NHC(O)-(C_1-C_4) alkyl-phenyl, N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-phenyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenylalkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy; and

L is -C_2-C_6 alkenyl-, or -C_2-C_6 alkynyl, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy.

6. A compound according to claim 5, wherein

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -C(O)N(R_9)-(C_1-C_4)alkyl-, -N(R_9)C(O) -(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-C(O)N(R_9)-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-N(R_9)C(O) -(C_1-C_4)alkyl-, -

$N(R_9)SO_2$-, $-SO_2N(R_9)$-, $-N(R_9)$-, $-N(R_9)-(C_1-C_4)$alkyl-, $-O-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-O-, or $-(C_1-C_4)$alkyl-$N(R_9)$-,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, $-SO_2$phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, $-(C_1-C_4)$alkyl-O-, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, quinolinyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, furanyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, or $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally

substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

7. A compound according to claim 6, wherein

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, benzyl, phenethyl, halogen, C_1-C_6 alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy;

L is -C_2-C_6 alkenyl-, or -C_2-C_6 alkynyl, each of which is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are

independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy; or

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl$-C(O)NR_9-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl$-$, $-N(R_9)C(O)-(C_1-C_4)$alkyl$-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)$alkyl$-$, $-O-(C_1-C_6)$alkyl$-$, $-(C_1-C_6)$alkyl$-O-$, or $-(C_1-C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, $-(C_1-C_4)$alkyl$-O-$, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkyl$-$, -alkenyl$-$, C(O);

R_1 is H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, or C_3-C_6 alkenyl;

R_2 is H, phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, $-(C_1-C_4)$ alkyl-pyridinyl, (C_1-C_4) hydroxyalkyl, wherein the phenyl ring is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, or pyrrolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, or $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl $-(C_1-C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide,

-phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl(C_1-C_6)alkyl, or $-SO_2$-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

8. A compound according to claim 1, which is (3*E*)-4-[4-((4-chlorobenzyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-2-(pyridin-3-ylmethyl)but-3-enoic acid;

(3*E*)-4-(4-{(4-*tert*-butylbenzyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-2-[3-(trifluoromethyl)benzyl]but-3-enoic acid; or

(3*E*)-4-{4-[[(3,4-dichlorophenyl)sulfonyl](4-isopropylbenzyl)amino]phenyl}-2-[3-(trifluoromethyl)benzyl]but-3-enoic acid.

9. A pharmaceutical composition comprising a compound according to any of claims 1-8 and at least one pharmaceutically acceptable carrier, solvent, adjuvant or excipient.

10. Use of a compound, or salt thereof, according to any of claims 1-8, or a composition according to claim 9, in the manufacture of a medicament for treating diabetes.

11. A method for inhibiting protein tyrosine phosphatase comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any of claims 1-8.

12. A method for treating metabolic disorders related to insulin resistance or hyperglycemia comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any of claims 1-8.

13. A process for preparing a compound according to any of claims 1-8.

14. A compound which is:

N-[4-(2-Bromoacetyl)-phenyl]-4-trifluoromethoxybenzenesulfonamide;

2-Pyridin-3-ylmethyl-malonic acid diallyl ester;

2-{2-oxo-2-[4-(4-trifluoromethoxybenzenesulfonylamino]-ethyl}-2-pyridin-3-ylmethyl-malonic acid diallyl ester;

4-{4-[(-Chlorobenzyl)-(4-trifluoromethoxybenzenesulfonyl)-amino]-phenyl}-4-oxo-2-pyridin-3-ylmethyl-butyric acid;

2-(3-Trifluoromethylbenzyl)-malonic acid diallyl ester;

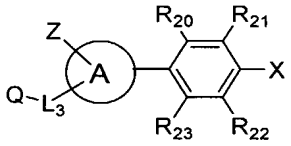
2-(2-{4-[(4-*tert*-Butylbenzyl)-(3,4-dichlobenzenesulfonyl)-amino]phenyl}-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester;

4-{4-[(4-tert-Butylbenzyl)-(3,4-dichlorobenzenesulfonyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid;

2-(2-{4-[(3,4-Dichlorobenzenesulfonyl-(4-isopropylbenzyl)-amino]-phenyl-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester; or

4-{4-[(3,4-dichlorobenzenesulfonyl)-(4-isopropylbenzyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid.

15. A compound of the formula:



where X is a functional group;

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, arylalkoxy, arylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, NH-aryl, -$N(C_1-C_4$ alkyl$)C(O)$aryl, -$NHC(O)$aryl, NHarylalkyl, $NHC(O)$-(C_1-C_4) alkyl-aryl, $N(C_1-C_4$ alkyl$)C(O)$-(C_1-C_4) alkyl-aryl, $N(C_1-C_4)$alkyl-aryl, -$NHSO_2$-aryl, -$N(C_1-C_4$alkyl$)SO_2$aryl, or -$N(C_1-C_4$alkyl)arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, furanyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, pyridyl, quinolinyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, CN, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, cycloalkyl, aryl, -aryl-carbonyl-aryl, -aryl-alkyl-aryl, -aryl-heteroaryl, -aryl-heterocycloalkyl, -heteroaryl, -heteroaryl-alkyl-aryl, -heterocycloalkyl, -aryl-O-aryl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, aryl$(C_1$-$C_6)$alkyl, alkanoyl, arylalkanoyl, alkoxycarbonyl, arylalkoxycarbonyl, heteroarylcarbonyl, heteroaryl, heterocycloalkylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, or $-SO_2$-aryl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, haloalkyl or haloalkoxy, and

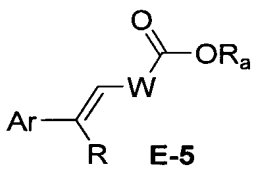
Z is absent, H, $-NHC(O)$aryl, $-N(C_1$-C_4 alkyl$)C(O)$aryl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, or NO_2, or

Z is $-NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl$, $-N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl$.

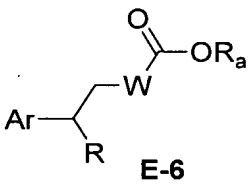
16. A compound according to claim 15 wherein, when L2 is a bond, the A ring is not phenyl.

17. A compound according to claim 15 or 16, wherein X is sulfonamido, carboxyl, $-CO_2R_e$ where R_e is C_1-C_6 alkyl or benzyl, aldehydo, keto, amido, nitro, anilino, hydroxyl, sulfide, or halo.

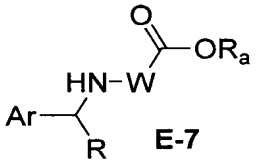
18. A compound of formula E-5, E-6, E-7, E-8, E-9, or E-10:



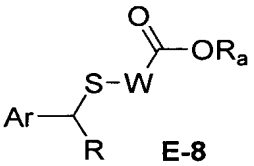
E-5



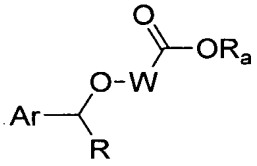
E-6



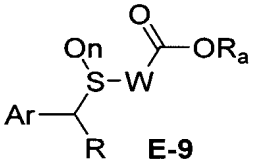
E-7



E-8



E-10



E-9

wherein:

R_a is hydrogen, C_1-C_6 alkyl, or benzyl; and

n is 1 or 2.

19. A method for preparing a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

tional application No
.../US2005/038939

A. CLASSIFICATION OF SUBJECT MATTER
C07C311/21 C07D213/55 C07C311/29 C07C69/612 A61K31/196
A61K31/4406 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DE 101 50 172 A1 (MORPHOCHEM AG) 30 April 2003 (2003-04-30) paragraph [0014]; claims; example 62	1,5-7, 9-13,19
X	WO 02/100341 A (WELLSTAT THERAPEUTICS CORPORATION; SHARMA, SHALINI; VON, BORSTEL, REID) 19 December 2002 (2002-12-19) page 17, line 16 - page 23, line 29; claims 92,153-160 example 52	1,5-7, 9-13,19

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[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2006	07/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seufert, G

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAJIMA, HISAO ET AL: "Preparation of phenylalkanoic acid derivatives as peroxisome proliferator-activated receptor controllers" XP002371578 retrieved from STN Database accession no. 1999:184126 abstract & WO 99/11255 A1 (ONO PHARMACEUTICAL CO., LTD., JAPAN) 11 March 1999 (1999-03-11) -----	1,5-7, 9-13,19
X	WO 00/64888 A (AVENTIS PHARMACEUTICALS PRODUCTS INC; JAYYOSI, ZAID; MCGEEHAN, GERARD,) 2 November 2000 (2000-11-02) claim 47: page 138, third compound in the right column, page 141, sixth compound in the right column, page 144, first compound in the right column, page 145, first column in the right column claims 53-87 -----	1,5-7, 9-13,19
X	BOUCHAIN G ET AL: "Development of Potential Antitumor Agents. Synthesis and Biological Evaluation of a New Set of Sulfonamide Derivatives as Histone Deacetylase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 46, 2003, pages 820-830, XP002278212 ISSN: 0022-2623 page 826, left-hand column, line 13 - line 27 page 828, right-hand column, line 24 - line 41 page 822, table 1, last compound in the right column -----	1,5-7,9, 13,19
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P,X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KITAMURA, YUSHI ET AL: "Hsp90 family protein inhibitor" XP002371590 retrieved from STN Database accession no. 2005:612072 abstract & WO 2005/063222 A1 (KYOWA HAKKO KOGYO CO., LTD., JAPAN) 14 July 2005 (2005-07-14)	1,5-7, 13,19

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002371589 Database accession no. BRN 1307336 abstract & F. D. KING, D. R. M. WALTON: SYNTHESIS, 1976, pages 40-42, -----	15-17
P,X	WO 2004/092146 A (THE INSTITUTES FOR PHARMACEUTICAL DISCOVERY, LLC; VAN ZANDT, MICHAEL,) 28 October 2004 (2004-10-28) examples 3,5,6 -----	14
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 11-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 18

Claim 18 refers to compounds of the general formulae E-5 to E-9. All of them include a variable "W", which has not been defined. Also no definition could be found in the description. Claim 18 is thus not sufficiently clear to carry out a meaningful search. Consequently, no search report has been established for claim 18 (Art. 17(2)(a) and (b) PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US2005/038939

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
/US2005/038939

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INTERNATIONAL SEARCH REPORT

International application No
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